

Short reports

Repeated therapy with monoclonal antibody to tumour necrosis factor α (cA2) in patients with rheumatoid arthritis

Michael J Elliott, Ravinder N Maini, Marc Feldmann, Alice Long-Fox, Peter Charles, Hanny Bijl, James N Woody

Our in-vitro, animal, and early clinical data suggest that tumour necrosis factor α (TNF α) is an important target for specific biological therapy in rheumatoid arthritis. We report the results of repeated treatment with a chimeric monoclonal antibody to TNF α (cA2) in patients having disease flares. 7 patients originally enrolled in an open-label trial completed two to four cycles, each of which was followed by a good clinical response, with median improvements in the swollen-joint count and C-reactive protein exceeding 80%. cA2 may be useful therapy in the control of acute disease flares in rheumatoid arthritis and treatment programmes including cA2 may be effective in the long-term management of this disease.

Lancet 1994; 344: 1125-27

Tumour necrosis factor α (TNF α) is important in inflammatory disease and may be a useful target for specific biological therapy in rheumatoid arthritis.¹ We reported beneficial effects in an open-label trial with a chimeric monoclonal antibody to TNF α (cA2).¹ In an accompanying article,² we report the results of a multicentre, randomised, double-blind placebo-controlled trial. cA2, at least in the short term, suppressed this inflammatory disease. Our experience to date shows that patients followed up for sufficient time eventually relapse,³ suggesting that repeated administration of the antibody will be required for maintenance of therapeutic effect. Here we report on the use of repeated therapy with cA2 at times of disease flare.

The retreatment programme included patients 1, 2, 3, 5, 7, 8, 9, and 10 from the open-label trial.¹ Patients received up to four cycles of treatment, the complete infusion protocol in the open trial being cycle 1. The timing of cycles 2-4 was dictated by disease relapse, defined as the loss of response to the previous cycle.¹ Most cycles were administered within 5 weeks of relapse, but cycle 2 was delayed in 4 patients for administrative reasons. Although 8 patients entered the retreatment programme, patient 5 was excluded from the analysis of response because of withdrawal for an adverse event during cycle 2 (see below). 3 patients were withdrawn after cycle 2. The response data therefore derive from 7 patients for cycles 1 and 2, 5 for cycle 3, and 4 for cycle 4. The total periods of observation, including periods of disease relapse, varied from 17 to 108 weeks.

cA2 is a human/murine chimeric monoclonal anti-TNF α antibody of IgG1 κ isotype, produced by Centocor,⁴ and was administered by intravenous infusion over 2-3 h. The dose was 20 mg/kg in cycle 1 (in two or four infusions) and 10 mg/kg in a single infusion for cycles 2-4. Patients were admitted overnight for cycle 1, but subsequently were treated as day cases.

Other drugs were maintained at stable dose from the beginning of cycle 1, except for some alterations after disease relapse between cycles 1 and 2: patient 3 took an increased dose of prednisolone for 1 week; patient 5 received a single intra-articular

injection of methylprednisolone; and patients 8 and 10 ceased their non-steroidal anti-inflammatory drugs. As in the open trial, additional steroids by any route were forbidden during the study, but simple analgesics were freely allowed.

The primary measure of response was the multi-variable Paulus index,⁵ calculated at two levels (Paulus 20% and 50%) and modified to accommodate the format of the data we collected.⁶ Laboratory measurements included the erythrocyte sedimentation rate (ESR, Westergren), C-reactive protein (CRP, rate nephelometry), and autoantibodies measured as described.¹ Human anti-chimeric A2 antibody responses (HACAs) were measured with a double-antigen enzyme immunoassay. False-positive signals due to rheumatoid factor anti-Fc antibodies were eliminated by the addition of covalently polymerised human Fc to the HACA sample diluent. Samples containing over 200 ng/mL cA2 (independent assay for free cA2) were considered likely to give a false-negative result for HACA, and were disqualified from analysis.

Each patient achieved a response to treatment cycle 1 and showed repeated responses after cycles 2-4, with maintenance of the response magnitude. The median maximum improvement in individual disease-activity assessments, such as the swollen-joint count and CRP, exceeded 80% after each cycle (data not shown). The median (interquartile range) swollen-joint counts before and the best assessment after each cycle were: (before,

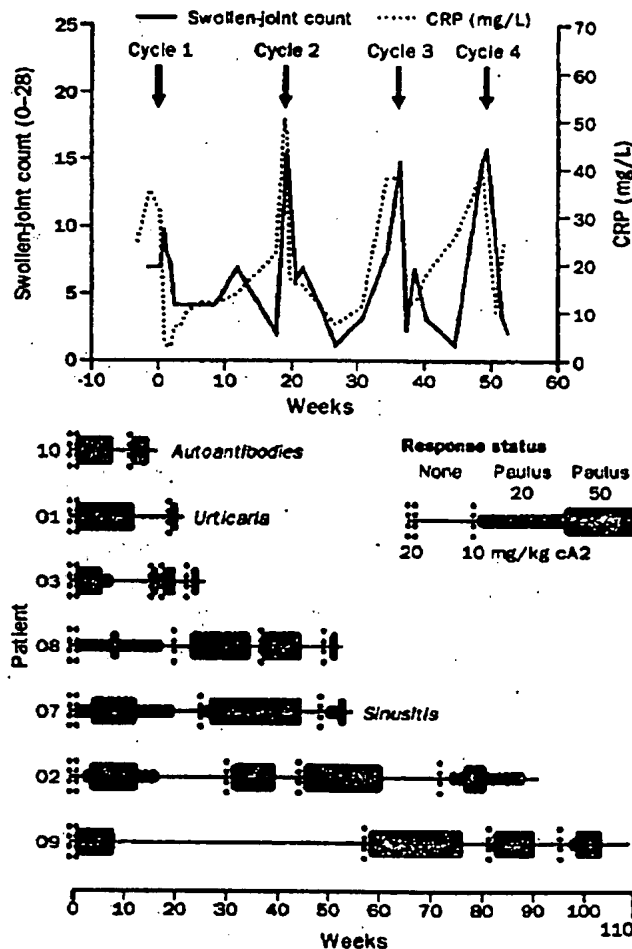


Figure: Responses to four successive cycles of cA2. Upper=swollen-joint count and CRP in patient receiving one cycle of 20 mg/kg cA2 and three cycles of 10 mg/kg cA2. Lower=response patterns in 7 patients who completed at least two full cycles of treatment with cA2. Adverse events resulting in early withdrawal are shown in italics.

Patient	Event	Time*	Relation to cA2
1	Urticaria	20/1 (C2)	Possibly
2	Anti-nuclear antibodies	48/4 (C3)	Probably
3	Pruritis	18/during (C3)	Possibly
5	Vasovagal syncope	16/during (C2)	Possibly
7	Chronic sinusitis	25/25 (C1)	Possibly
8	Eczema	32/13 (C2)	Possibly
	Pharyngitis	51/2 (C4)	Possibly
9	Urinary tract infection	58/1 (C1)	Possibly
	Anti-nuclear antibodies	61/4 (C2)	Probably
	Flushing, headache, fever (38°C)	85/during (C4)	Probably
10	dsDNA and cardiolipin antibodies	6/6 (C1)	Probably

*Weeks after cycle 1/weeks after last cycle: C=last cycle number. dsDNA=double-stranded DNA. Only events considered reasonably related to cA2 included. All events resolved completely, except for eczema in patient 8 and laboratory changes in 9.

Table: Adverse events

after) cycle 1, 21 (16-25), 3 (0-3) ($p=0.011$ by Wilcoxon's signed-ranks test); cycle 2, 16 (8-21), 2 (0-4) ($p=0.011$); cycle 3, 8 (6.5-18.5), 1 (1-3) ($p=0.03$); and cycle 4, 11 (10.3-14.8), 2 (2-6.5) ($p>0.05$). Equivalent data for CRP were: cycle 1, 31 mg/L (10-44, normal <10 mg/L), 0 (0-5) ($p=0.011$); cycle 2, 49 (24-62), 3 (2-7) ($p=0.011$); cycle 3, 39 (24-69.5), 0 (0-17.5) ($p=0.03$); and cycle 4, 40.5 (11.5-125), 5 (0-65.5) ($p>0.05$).

The overall pattern of response in a patient who completed all four cycles is shown in the figure (A). Note the co-ordinated change in swollen-joint count and CRP.

Analysis of possible changes in the duration of the response was complicated by the dose reduction in cycles 2-4 and the change from a multiple-divided-dose infusion in cycle 1 to a single infusion later. Individual patients showed varying response patterns (figure, B) but overall, the duration tended to shorten with successive cycles. The median Paulus 20% response duration after treatment with 20 mg/kg cA2 in cycle 1 was 12 weeks (interquartile range 8-17.4). Equivalent values for cycles 2-4 (when patients received half this dose) were 9.1 weeks (1-19.1), 8.3 weeks (3.2-12.5), and 7.7 weeks (1.6-15.2) ($p>0.05$ compared with cycle 1 by Friedman's test, repeated Wilcoxon's signed-ranks tests, and linear regression).

41 infusions were administered in this study and were well tolerated, with 2 exceptions. Patient 5 was withdrawn after the administration of only 1% of the scheduled cA2 dose in cycle 2. This followed an episode of vasovagal syncope, consequent on a traumatic venepuncture. Patient 9 developed fever, headache, and transient facial flushing during cycle 4, but was treated symptomatically and not withdrawn. Other adverse events that were considered reasonably related to cA2 are outlined in the table. 3 events prompted the precaution of early withdrawal (patients 1, 7, and 10).

4 patients had no HACA responses when tested at least 6 weeks after the last infusion. The remaining 4 patients developed HACAs at varying times after retreatment (titres 10, 20, 80, and 640 in patients 3, 1, 5, and 9, respectively), all specific for the murine variable region of cA2. Of these, 2 patients completed all four cycles, 1 completed two cycles, and 1 was withdrawn during cycle 2. Some patients with HACAs showed a reduction in response duration in cycles 2-4. In other patients, however, no clear relation was evident. Patient 9 developed a high-titre HACA (640) after cycle 2, but her cycle 3 response duration of 8.7 weeks was no different from her cycle 1 duration (8 weeks). Conversely, no HACA was detected in patient 8, but her response duration fell from 17.4 weeks in cycle 1 to 8.3 in cycle 3.

The data show that patients with flares of rheumatoid arthritis can be successfully managed with cA2, which

provides an alternative to traditional treatments such as hospital admission, high-dose corticosteroids, or cytotoxic therapy. Our requirement for disease relapse before retreatment represented a difficult therapeutic challenge. Despite this, we achieved a response after each patient/cycle, with impressive improvements in clinical and laboratory measures of inflammation. Our success in demonstrating repeated responses in the same individuals suggests that regular treatment with cA2 may achieve long-term disease suppression.

The adverse events included the development of antinuclear antibodies in 3 of our 7 patients. Although two of these findings were unassociated with specific autoantibodies, patient 10 developed significant titres of dsDNA and cardiolipin antibodies after cycle 1,² and showed a further rise in titres after cycle 2. Although no clinical features of systemic lupus erythematosus developed, we withdrew her from study. We also adopted a cautious approach to minor infective events, withdrawing patient 7 after the development of sinusitis. With more experience in the repeated use of cA2, a lower dropout rate may be achievable.

Only 1 of 20 patients in the original open-label trial developed an antiglobulin response, suggesting that cA2 is not especially immunogenic. HACAs specific for the murine portion of cA2 were eventually detected in half of the patients in the retreatment programme. These were mostly low titre and 2 patients were successfully retreated despite their presence. Similar antiglobulin responses were seen in 3 of 4 rheumatoid arthritis patients treated with repeated injections of a humanised monoclonal antibody to CDw52,³ suggesting that antibody reshaping does not entirely eliminate immunogenicity. Whether the development of HACAs in our patients contributed to adverse events is unknown.

Several strategies could be adopted to prevent the development of antiglobulin responses to cA2, including combination therapy with traditional immunosuppressive drugs or the co-administration of specific, T-cell-directed monoclonal antibodies with the aim of inducing tolerance.⁴ Anti-TNF and anti-CD4 were synergistic in the control of murine collagen-induced arthritis, and antiglobulin responses to the TNF blocking antibody were reduced.⁵ The application of such combination immunotherapy deserves further investigation in man.

The Kennedy Institute is supported by a core grant from the Arthritis and Rheumatism Council of Great Britain. This trial was funded by Centocor, of which Dr J N Woody and Dr J A Bli are employees. Prof M Feldmann is a consultant for Centocor and received research support as well as support for special laboratory procedures for this study from Centocor.

We thank Mr Dave Zellinger for statistical advice and the following for their help: Ms Annette Winter, Ms Allison Potter, Ms Gail Harris, and the nursing staff on wards 5 West and 9 South, Charing Cross Hospital.

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Kennedy Institute of Rheumatology, Hammermith, London W6 7DW, and Academic Department of Rheumatology, Charing Cross and Westminster Medical School, London, UK; (M J Elliott MD, Prof R N Maini FRCP, Prof M Feldmann MD, A Long-Fox MD, P Charles FRCS); and Centocor Inc, Malvern, Pennsylvania, USA (J A Bijl MD, J N Woody MD)

Correspondence to: Prof Ravinder N Maini

Botulinum toxin for chronic anal fissure

D Gul, E Cassetta, G Anastasio, A R Bentivoglio, G Maria, A Albanese

Botulinum toxin can chemically denervate striated muscle. Botulinum toxin A (15 U) was used to treat ten patients with chronic anal fissure by injection in the internal sphincter. In seven patients, the lesion healed at 2 months after treatment; one relapsed at 3 months. In one patient the lesion healed at 1 month, but partly relapsed a month later. Mild faecal incontinence lasting for 1 day was observed in one patient. We propose that botulinum toxin injections in the internal anal sphincter be considered an alternative approach to surgical therapy of anal fissure.

Lancet 1994; 344: 1127-28

Unlike the acute fissure, chronic anal fissure is not usually self-limiting¹ and its pathophysiology is not completely understood.² Hypertonicity of the internal anal sphincter may be involved.³ The recommended treatments are anal dilation or lateral internal sphincterotomy, which are successful in 85-95% of patients. Internal sphincterotomy permanently weakens the sphincter, which may be associated with incontinence, infection, and anal deformity.⁴

Chemical denervation with botulinum toxin is a versatile tool for targeted weakening of striated muscles.^{5,6} The toxin

may also weaken smooth muscle in the gastrointestinal tract.⁷ We have evaluated local injections of botulinum toxin to reduce hypertonus of the internal anal sphincter and induce healing in patients with idiopathic anal fissure.

Ten consecutive outpatients (mean age 42.4, range 24-82) with chronic idiopathic anal fissure gave informed written consent for study (table). They had had symptoms for a mean of 19.65 (SE 3.52) months. All had typical features of chronic anal fissure: posterior anal fissure, with a large sentinel tag of skin and the exposure of fibres of the internal sphincter; and post-defaecatory pain for over 2 hours. No patient had nocturnal pain. All patients were advised to eat food with high-fibre content and received a prescription for laxatives. No patient was treated with topical anaesthetic agents before or during study.

Anal manometry at rest and after maximum voluntary contraction was done before treatment and at each follow-up. The normal range for our laboratory is 66 (23) and 144 (60) mm Hg, respectively.⁸ Type A botulinum toxin (Botox, Allergan) was diluted in saline to 50 U/mL. The anal sphincter was easily palpated and injected with a 27 G needle. Every patient received three injections of 5 U (0.1 mL) each within the contracted muscle; two injection sites were located laterally, the other posteriorly. No anaesthesia was used during the 5 minute procedure. The patients were evaluated 1 week, 1 month, and 2 months after treatment by anoscopy, anal manometry, and a clinical evaluation. At each visit the patients were asked whether, despite any local pain, they wanted to stay in the study. If not, they were offered anal sphincterotomy.

Efficacy (strength of internal and external anal sphincters) was evaluated by multifactorial analysis of variance, by comparison of resting anal pressure or maximum voluntary pressure before treatment with post-injection values. The time course of variations in the two pressures was analysed by *t* test.

1 week after treatment, all patients still had fissure. Post-defaecatory pain had disappeared in five patients and reduced in four. Pain during exploration had disappeared in five and was reduced in the others. Compared with baseline, resting pressure was reduced by 25.2% ($p < 0.05$). Maximum voluntary pressure, although lower on average, did not differ statistically from baseline (table).

Inspection at 1 month after treatment revealed a healing scar in six patients. Compared with pretreatment records, post-defaecatory pain had disappeared in seven patients and was reduced in one; pain during exploration had disappeared in six and was lower in one. Compared with baseline, resting pressure was reduced by 23.9% ($p < 0.05$), whilst voluntary pressure was unchanged. The two pressures were not significantly different from 1 week values.

At 2 months, seven patients had a healing scar. The fissure was observed again in patient 5, who had had a healing scar at 1 month. Her subjective symptoms, however, were mild. Compared with pretreatment, post-defaecatory pain had disappeared in seven patients and was

Patient (age/sex)	Duration (mo)	Inspection			Outcome	Resting pressure (mm Hg)				Maximum voluntary pressure (mm Hg)			
		1 wk	1 mo	2 mo		Baseline	1 wk	1 mo	2 mo	Baseline	1 wk	1 mo	2 mo
1 (24/F)	9	Fissure	Healing	Healing	Healing	90	60	50	50	76	65	40	50
2 (43/F)	12	Fissure	Healing	Healing	Healing	85	80	50	75	45	30	25	20
3 (43/F)	36	Fissure	Fissure	Fissure	Ineffective	85	80	80	80	60	25	60	60
4 (25/M)	1.5	Fissure	Fissure	Healing	Healing	75	65	50	85	50	25	40	100
5 (45/F)	18	Fissure	Healing	Fissure	Relapse	60	50	40	85	25	12	15	25
6 (27/M)	12	Fissure	Healing	Healing	Relapse	80	75	75	90	50	90	90	100
7 (50/M)	20	Fissure	Healing	Healing	Healing	80	60	40	40	85	85	100	100
8 (28/M)	24	Fissure	Healing	Healing	Healing	60	45	50	70	100	50	100	100
9 (82/F)	3	Fissure	Fissure	Fissure	Ineffective	95	45	100	100	20	10	30	30
10 (57/F)	1	Fissure	Fissure	Healing	Healing	65	50	55	40	20	25	30	25
Mean (SE)	77.5 (3.89)	58 (3.69)	59 (6.18)	71.5 (6.71)	53 (8.69)	41.7 (9.24)	53.8 (10.03)	61 (11.27)

Table: Clinical outcome, and manometry